1. (Amended) An antibody-based fusion protein comprising at least a portion of a CH2 domain required for immunoglobulin protection receptor (FcRp) binding affinity, linked to a non-Ig protein, wherein said CH2 domain is an IgG1 or an IgG3 CH2 domain comprising a mutation or a deletion that reduces binding affinity for an Fc receptor, and said antibody-based fusion protein has a longer circulating half-life *in vivo* than an antibody-based fusion protein without said mutation or deletion.

2. (Amended) An antibody-based fusion protein comprising at least a portion of a CH2 domain linked to a non-Ig protein, wherein said CH2 domain is an IgG2 CH2 domain, and said antibody-based fusion protein has a longer circulating half-life *in vivo* than an antibody-based fusion protein comprising a portion of an IgG1 CH2 domain linked to said non-Ig protein.

27. (New) An antibody-based fusion protein comprising a variable domain and a portion of a CH2 domain linked to the N-terminus of a non-Ig protein, wherein said CH2 domain is an IgG4 CH2 domain, and said antibody-based fusion protein has a longer circulating half-life *in vivo* than an antibody-based fusion protein comprising a portion of an IgG1 CH2 domain linked to said non-Ig protein.

REMARKS

In the Office action, claims 1-26 were considered. Claims 14-24 and 26 were withdrawn. Claim 25 was objected to. Claims 1 and 5 were rejected under 35 U.S.C. § 112. Claims 1, 3, 4, 6-13 and 25 were rejected under 35 U.S.C. § 102. Claim 2 was rejected under 35 U.S.C. § 103(a). Claims 1 and 2 have been amended, claims 5 and 25 have been canceled without prejudice, and new claim 27 has been added. Upon entry of this amendment, claims 1-4, 6-13, and 27 will be pending in this application.

Amendments To The Claims

The claims have been amended to further clarify the claimed subject matter. Basis for the claim amendments can be found in the specification, including the claims as originally filed. Specifically, basis for the recitation in claim 1 of a fusion protein comprising a portion of a CH2 having binding affinity for an immunoglobulin protection receptor (FcRp) can be found, *inter alia,* in original claim 5, and in the specification at least at lines 13-24 of page 8. Basis for new claim 27 can be found, *inter alia,* in original claim 2.

Applicants submit that these amendments introduce no new matter.

Claim Objections And Rejections

The following comments address claim objections and rejections in the order that they were raised in the Office Action.

Claim Objection

Claim 25 was objected to because of its dependence on a non-elected claim. Claim 25 has been canceled without prejudice, thereby obviating this objection.

Rejection under 35 U.S.C. § 112

Claims 1 and 5 were rejected under 35 U.S.C. 112, second paragraph. Claims 1 and 5 were rejected for reciting the term "substantially." Claim 1 has been amended to delete "substantially" and claim 5 has been canceled without prejudice, thereby obviating the rejections based on the use of this term.

Claim 5 was also rejected for reciting the term "immunoglobulin protection receptor." Claim 5 has been canceled without prejudice, thereby obviating this rejection. However, claim 1 has been amended to recite an immunoglobulin protection receptor (FcRp). Applicants respectfully submit that "FcRp" is well-defined in the art of molecular immunology, as disclosed on page 8, lines 13-24 of the specification. Accordingly, Applicants respectfully submit that "FcRp" distinctly identifies a protein.

Therefore, Applicants respectfully request that the rejections under 35 U.S.C. § 112 be reconsidered and withdrawn.

Rejection under 35 U.S.C. §102

Claims 1, 3, 6-9, 13 and 25 were rejected under 35 U.S.C. §102(b) as being anticipated by Hoogenboom et al., Molecular Immunology, Vol. 28, No. 9, pp. 1027-1037 (1991) (hereinafter Hoogenboom et al.).

Claim 1 has been amended to include a feature of now canceled claim 5, which was not rejected under 35 U.S.C. §102(b) in view of Hoogenboom et al. Claim 25 has been canceled without prejudice. Amended claim 1 recites a fusion protein comprising a portion of a CH2 domain with FcRp binding affinity, wherein the CH2 domain is an IgG1 or an IgG2 CH2 domain with a mutation or deletion that reduces affinity for an Fc receptor.

Applicants respectfully submit that these limitations are not disclosed in Hoogenboom et al. The Office action points to a fusion construct described on page 1029, column 2, second paragraph of Hoogenboom et al. Applicants respectfully submit that this construct retains only the first 3 amino acids of an IgG1 CH2 domain and thus, does not contain a portion of a CH2 domain required for FcRp binding affinity (see, *inter alia*, at least lines 13-24 on page 8 of the specification). Accordingly, Hoogenboom et al. does not disclose every element of the pending claims as amended herein, and does not form the proper basis for continued rejection of claims 1, 3, 6-9, and 13 under 35 U.S.C. §102(b).

Claims 1, 4, 7-8, and 10-13 were rejected under 35 U.S.C. § 102(a) as being anticipated by WO 97/30089.

As discussed above, claim 1 has been amended to include a feature of now canceled claim 5, which was not rejected under 35 U.S.C. §102(a) in view of WO 97/30089. Accordingly, Applicants respectfully submit that WO 97/30089 also fails to disclose the limitations of amended claim 1. Specifically, WO 97/30089 fails to disclose a fusion protein comprising a portion of a CH2 domain having binding affinity for FcRp but with a mutation or deletion that reduces binding affinity for an Fc receptor. Accordingly, WO 97/30089 does not disclose every element of the pending claims as amended herein, and does not form the proper basis for continued rejection of claims 1, 4, 7-8, and 10-13 under 35 U.S.C. § 102(a).

Therefore, Applicants respectfully request reconsideration and withdrawal of all the rejections under 35 U.S.C. §102.

Rejections under 35 U.S.C. §103

Claim 2 was rejected under 35 U.S.C. §103(a) as being unpatentable over Hoogenboom et al. in view of U.S. Patent No. 6,100,387 to Herrmann et al. (the '387 patent). The Office action pointed to the disclosure in the '387 patent of a "chemokine-encoding fragment ... containing a linker and part of the Fc portion of the IgG4 gene" (page 5 of the Office action).

Claim 2 has been amended to include an IgG2 CH2 domain, but not an IgG4 CH2 domain. However, Applicants respectfully traverse this rejection to the extent that it is applied to amended claim 2 and new claim 27 which does include an IgG4 CH2 domain.

Applicants submit that the presently claimed invention relates to an antibody-based fusion protein with an increased serum half-life. The fusion protein of new claim 27 specifically includes a variable domain and a portion of an IgG4 CH2 domain that increases the *in vivo* circulating half-life of the fusion protein compared to the circulating half-life of a fusion protein with a portion of an IgG1 CH2 domain. New claim 27 also recites that a non-Ig protein is linked via its N-terminus to the Ig portion of the fusion protein.

In contrast, Applicants submit that Hoogenboom et al. discloses a fusion protein having an IgG1 CH2 domain, and the '387 patent discloses a non-Ig protein linked via its C-terminus to an Fc portion of an IgG4.

Applicants submit that neither of the cited references teaches, suggests, or motivates their combination to obtain the fusion protein of new claim 27. Specifically, the cited references fail to teach or suggest using an IgG4 CH2 domain in a fusion protein having a variable region. The cited references also fail to teach or suggest linking an IgG4 CH2 domain to the N-terminus of a non-Ig protein. Therefore, the combination of references is improper, and Applicants respectfully request reconsideration and withdrawal of this rejection.

Furthermore, Applicants submit that even if the cited references were combined as suggested, they provide no expectation of successfully producing the claimed antibody-based

fusion proteins with an enhanced circulating half-life. Applicants submit that the references fail to teach or suggest that the use of a CH2 domain with reduced Fc receptor binding would enhance the *in vivo* circulating half-life of an antibody-based fusion protein. Indeed, it is the present specification that teaches "that fusing a second protein, such as a cytokine, to an immunoglobulin may alter the antibody structure, resulting in an increase in binding affinity for one or more of the cell-bound Fc receptors and leading to a rapid clearance of the antibody-based fusion protein from the circulation" (page 7, line 2-5 of the specification). Therefore, Applicants submit that it is the present specification that provides the expectation of success, in addition to the motivation, suggestion, and teaching, for increasing the *in vivo* circulating half-life of an antibody-based fusion protein by using a portion of a CH2 with reduced Fc receptor binding affinity. Accordingly, without a teaching or motivation to combine the references and no expectation of successfully providing that which Applicants claim, Applicants respectfully submit that their claimed invention, considered as a whole, is unobvious over the cited references and request reconsideration and withdrawal of this rejection.

Therefore, Applicants submit that the cited references do not form the proper basis for continued rejection of claims 2 and 27 under 35 U.S.C. §103(a) and respectfully request that all the rejections under 35 U.S.C. §103(a) be reconsidered and withdrawn.

CONCLUSION

Applicants submit that on the basis of the foregoing remarks and claim amendments, claims 1-4, 6-13, and 27 are in condition for allowance. Should any further issues of patentability be determined to exist, the Examiner is invited to contact the undersigned by telephone to expedite prosecution of this application.

Respectfully submitted,

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CLAIM AMENDMENTS (RED-LINED VERSION)

1. (Amended) An antibody-based fusion protein [with an enhanced circulating half-life,] comprising at least a portion of a CH2 domain required for immunoglobulin protection receptor (FcRp) binding affinity, [an immunoglobulin (Ig) heavy chain having substantially reduced binding affinity for an Fc receptor, said portion of heavy chain being] linked to a [second] non-Ig protein, wherein said CH2 domain is an IgG1 or an IgG3 CH2 domain comprising a mutation or a deletion that reduces binding affinity for an Fc receptor, and said antibody-based fusion protein [having] has a longer circulating half-life *in vivo* than an antibody-based fusion protein without said mutation or deletion [unlinked second non-Ig protein].

2. (Amended) An [The] antibody-based fusion protein comprising at least a portion of a CH2 domain linked to a non-Ig protein [of claim 1], wherein said [portion of heavy chain comprises at least the] CH2 domain is [of] an IgG2 CH2 domain [or IgG4 constant region], and said antibody-based fusion protein has a longer circulating half-life *in vivo* than an antibody-based fusion protein comprising a portion of an IgG1 CH2 domain linked to said non-Ig protein.

27. (New) An antibody-based fusion protein comprising a variable domain and a portion of a CH2 domain linked to the N-terminus of a non-Ig protein, wherein said CH2 domain is an IgG4 CH2 domain, and said antibody-based fusion protein has a longer circulating half-life *in vivo* than an antibody-based fusion protein comprising a portion of an IgG1 CH2 domain linked to said non-Ig protein.